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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	ZOLTAN KISS	**Examiner:**	Krass, Fredrick
Issue Date:	June 29, 2004	**Group Art Unit:**	1614
Patent No.:	6,756,063 B2		
Appln. No.:	09/864,685	**Docket No.**	54938-236531
Filing Date:	May 24, 2001		
Title:	METHODS AND COMPOSITIONS FOR THE TREATMENT OF HUMAN AND ANIMAL CANCERS		

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Karen Hull
Karen Hull

REQUEST FOR EXPEDITED ISSUANCE OF CERTIFICATE OF CORRECTION OF PATENT UNDER 37 C.F.R. § 1.322

The enclosed Certificate of Correction (PTO/SB/44) is submitted to correct errors in this patent arising as a result of an Office mistake.

No fee is believed to be necessary. Should any fee be required, the Commissioner is authorized to charge our Deposit Account No. 06-0029 and is requested to notify us of the same.

The corrections referenced on PTO/SB/44 are typographical. The correction to claim 2 is referenced in the Amendment filed on July 11, 2003, page 5. The corrections to claims 8 (claim 31 in the amendment) and 15 (claim 39 in the amendment) are referenced in the Amendment filed on October 22, 2003, pages 3 and 4. Copies of the Amendments are attached.

Respectfully Submitted,

ZOLTAN KISS

Dated: August 4, 2004

Certificate
AUG 12 2004
of Correction

By: Sean Mahoney

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PTO/SB/44 (02-01)
Approved for use through 01/31/2004. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : 6,756,063 B2

DATED : June 29, 2004

INVENTOR(S) : ZOLTAN KISS

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Claim 2, Line 50, that portion of the formula reading "C(—S)" should read -- C(=S) --.

Claim 8, line 28 delete the word "L-buthionine-SR-sulfoximine," and replace it with:
-- L-buthionine-S,R-sulfoximine, --

Claim 15, line 55 delete the word "2-cyclohexene-1-one" and replace it with:
-- 2-cyclohexene-1-one, --

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PATENT NO. 6,756,063 B2

No. of additional copies

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	ZOLTAN KISS	**Examiner:**	Krass, Frederick F.
Serial No.:	09/864,685	**Group Art Unit:**	1643
Filed:	May 24, 2001		
For:	METHODS AND COMPOSITIONS FOR THE TREATMENT OF HUMAN AND ANIMAL CANCERS	**Docket No.**	54938-236531

Mail Stop Fee Amendment
Commissioner for Patents
P. O. Box 1450
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I CERTIFY THAT, ON JULY 11, 2003, THIS PAPER IS BEING SENT VIA FACSIMILE TO THE COMMISSIONER FOR PATENTS, P. O. BOX 1450, ALEXANDRIA, VA 22313-1450.

Jolene M. Alger

AMENDMENT

INTRODUCTORY COMMENTS

This Amendment is responsive to the outstanding Office Action mailed March 13, 2003. A petition and fee for a one-month extension of time is included herewith. A fee for additional claims is also included. If any additional fee is required for entry of this paper, the Commissioner is authorized to charge our Deposit Account 06-0029 and is requested to notify us of the same.

AMENDMENTS TO THE SPECIFICATION

Please amend the specification as follows:

Please replace the paragraph entitled "Cross Reference to Related Application" on page 1 of the specification with the following paragraph:

This application claims ~~priority to US~~ the benefit of U.S. Provisional Application 60/279,859, entitled METHODS AND COMPOSITIONS FOR THE TREATMENT OF HUMAN AND ANIMAL CANCERS, filed on March 29, 2001~~, Serial No. _____ (Attorney Docket No. 54938-226916)~~.

On page 3 of the specification, please replace the second full paragraph (beginning at line 17) with the following paragraph:

In one aspect of the invention, compositions of the present invention are prepared by incorporating one or more of the components A, B, C, and D into the composition. The dithiocarbonyl component A, preferably a dithiocarbamate compound, of the composition usually has the formula: ~~$(R_1)_m(R_2)$-Z-C-S-S-Y~~ $(R_1)_m(R_2)$–Z–C(S)–S–Y wherein m is 0 or 1, but other structures can be envisioned. For example, a dithiocarbamate moiety can be inserted into fatty acid chains, or between the phosphate group and the polar headgroup, or at the end of the polar headgroup in a phospholipid molecule.

On page 11 of the specification, please replace the second full paragraph (beginning at line 7) with the following paragraph:

Component A, the dithiocarbonyl compounds, particularly dithiocarbamates, of the present invention generally have the formula: ~~$(R_1)_m(R_2)$Z-C-S-S-Y~~ $(R_1)_m(R_2)$–Z–C(S)–S–Y, wherein m is 0 or 1.

On page 15 of the specification, please replace the second full paragraph (beginning at line 10) with the following paragraph:

Other preferred dithiocarbonyl components for use in the compositions of the present invention are dimers of the dithiocarbonyl compounds described previously. Such dimers may be represented by the formula: ~~$(R_1)_m(R_2)Z-C-S-S-C-Z(R_1)_m(R_2)$~~ $(R_1)_m(R_2)Z-C(S)-S-S-C(S)-Z(R_1)_m(R_2)$. A preferred embodiment is Disulfuram, which is a dimer of DEDC currently used for the treatment of alcohol abuse.

On page 25 of the specification, please replace the first full paragraph (beginning at line 5) with the following paragraph:

The ability of the compositions to alter the viability of a broad range of cancerous cell types, while inducing less changes in minimally affecting the viability of noncancerous cells, are set forth in detail in Examples ~~1-23~~ 1-24 below.

On page 37 of the specification, please replace the heading beginning at line 25 with the following heading:

Examples ~~20 and~~ 21 and 22. In vivo HT-29 human colon carcinoma and ~~HT-18~~ HT-168 human melanoma mouse xenografts.

On page 39 of the specification, please replace the heading beginning at line 21 with the following heading:

Example ~~22~~ 23. Western blot analysis of apoptotic gene product expression in cancer cells.

On page 40 of the specification, please replace the heading beginning at line 14 with the following heading:

Example ~~23~~ 24. In vivo acute toxicological investigations.

AMENDMENTS TO THE CLAIMS

1. (Currently amended) A composition capable of inducing apoptosis or necrosis in cancer cells, comprising:

a ~~dithiocarbonyl~~ dithiocarbamate compound;

a metal cation selected from the group consisting of Zn^{++} and Cu^{++};

a modulator of cellular glutathione effective to decrease cellular glutathione levels; and

~~an inhibitor of the phosphorylation of choline~~ dimethylethanolamine.

2. (Currently amended) The composition of claim 1, wherein the ~~dithiocarbonyl~~ dithiocarbamate compound has the formula:

~~$(R_1)_m(R_2)Z$-C-S-S-Y~~, $(R_1)(R_2)N-C(=S)-S-Y$,

~~wherein m is 0 or 1,~~

~~wherein Z is O or N, but if Z is O, then m is 0; and~~

wherein R_1 and R_2 may be independently selected from the group consisting of hydrogen, ~~or~~ C1-C24 straight, branched, or cyclic alkyl, alkenyl, aryl, acyl, alkaryl, aralkyl, ~~or~~ and alkoxy groups, ~~said groups~~ optionally substituted with ester, ether, halogen, sulfate, hydroxy, or phosphate groups, and wherein R_1 and R_2 may be optionally connected via a bridge comprising $-(CH_2)_n-$, wherein n is 3-8, and wherein said bridge may be optionally substituted independently on any of the carbon atoms with C1-C10 straight, branched, or cyclic alkyl, aryl, aryalkyl, or alkaryl groups, each of said groups optionally substituted with hydroxy, halo, phosphate, sulfate, or sulfonate groups; and

wherein Y is chosen from the group consisting of hydrogen, a pharmaceutically acceptable cation, a physiologically cleavable leaving group, a targeting moiety, ~~or~~ and a chemotherapeutic drug.

3. (Currently amended) The composition of claim ~~2~~ 1, wherein the ~~dithiocarbonyl~~ dithiocarbamate compound is selected from the group consisting of: diethyldithiocarbamate ~~(DEDC)~~; ~~tricyclo [5.2.1.$O^{2,6}$] decyl-9[8]-xanthogenate (D609);~~

tetraethylthiuram disulfide ~~(Disulfuram, $((C_2H_5)_2NCS_2]_2)$)~~; and pyrrolidinedithiocarbamate ~~(PDC)~~.

4. (Currently amended) The composition of claim ~~3~~ 1, wherein the ~~dithiocarbonyl~~ dithiocarbamate is ~~PDC~~ pyrrolidinedithiocarbamate.

5. (Cancelled)

6. (Original) The composition of claim 1, wherein the metal cation is Zn^{2+}.

7. (Original) The composition of claim 1, wherein the modulator of cellular glutathione is selected from the group consisting of ethacrynic acid, L-buthionine-S,R-sulfoximine, diethylmaleate, 2-cyclohexene-1-one, and 1-chloro-2,4-dinitrobenzene.

8. (Original) The composition of claim 1, wherein the modulator of cellular glutathione is ethacrynic acid.

9. (Cancelled)

10. (Currently amended) The composition of claim 1, wherein the ~~dithiocarbonyl~~ dithiocarbamate compound is ~~PDC~~ pyrrolidinedithiocarbamate in a concentration range of about 5-200 μM, wherein the metal cation is Zn^{2+} in a concentration range of about 20-500 μM, wherein the modulator of cellular glutathione ~~levels~~ is ethacrynic acid in a concentration range of about 10-300 μM, and wherein ~~the inhibitor of the phosphorylation of choline is~~ dimethylethanolamine is in a concentration range of about 3-40 mM.

11. – 30. (Cancelled)

31. (New) A composition capable of inducing apoptosis or necrosis in cancer cells, comprising:

a biologically effective amount of a dithiocarbamate compound; and

a biologically effective amount of a modulator of cellular glutathione effective to decrease cellular glutathione levels.

32. (New) The composition of claim 31, wherein the dithiocarbamate compound is pyrrolidinedithiocarbamate.

33. (New) The composition of claim 31, wherein the modulator of cellular glutathione is selected from the group consisting of ethacrynic acid, L-buthionine-S,R-sulfoximine, diethylmaleate, 2-cyclohexene-1-one, and 1-chloro-2,4-dinitrobenzene.

34. (New) The composition of claim 31, wherein the modulator of cellular glutathione is ethacrynic acid.

35. (New) The composition of claim 31, wherein the dithiocarbamate compound is pyrrolidinedithiocarbamate, and the modulator of cellular glutathione is ethacrynic acid.

36. (New) The composition of claim 35, comprising about 10 to about 50 μM pyrrolidinedithiocarbamate, and about 10 to about 50 μM ethacrynic acid.

37. (New) The composition of claim 35, comprising about 20 μM pyrrolidinedithiocarbamate, and about 10 μM ethacrynic acid.

38. (New) The composition of claim 31, further comprising a biologically effective amount of dimethylethanolamine.

39. (New) A composition capable of inducing apoptosis or necrosis in cancer cells, comprising:

a biologically effective amount of a dithiocarbamate compound;

a biologically effective amount of a modulator of cellular glutathione effective to decrease cellular glutathione levels; and

a biologically effective amount of a metal cation selected from the group consisting of Zn^{++} and Cu^{++}.

40. (New) The composition of claim 39, wherein the dithiocarbamate compound is pyrrolidinedithiocarbamate.

41. (New) The composition of claim 39, wherein the modulator of cellular glutathione is selected from the group consisting of ethacrynic acid, L-buthionine-S,R-sulfoximine, diethylmaleate, 2-cyclohexene-1-one, and 1-chloro-2,4-dinitrobenzene.

42. (New) The composition of claim 39, wherein the modulator of cellular glutathione is ethacrynic acid.

43. (New) The composition of claim 39, wherein the metal cation is Zn^{++}.

44. (New) The composition of claim 39, comprising about 5 to about 50 μM pyrrolidinedithiocarbamate, about 50 to about 200 μM Zn^{++}, and about 10 to about 100 μM ethacrynic acid.

45. (New) The composition of claim 39, comprising about 10 to about 50 μM pyrrolidinedithiocarbamate, about 30 to about 80 μM Zn^{++}, and about 30 to about 80 μM ethacrynic acid.

46. (New) A composition capable of inducing apoptosis or necrosis in cancer cells, comprising:

a biologically effective amount of a dithiocarbamate compound;

a biologically effective amount of a metal cation selected from the group consisting of Zn^{++} and Cu^{++}; and

a biologically effective amount of dimethyethanolamine.

47. (New) The composition of claim 46, wherein the dithiocarbamate compound is pyrrolidinedithiocarbamate.

48. (New) The composition of claim 46, wherein the metal cation is Zn^{++}.

49. (New) A composition capable of inducing apoptosis or necrosis in cancer cells, comprising:

tricyclo-[5.2.1.$O^{2,6}$]-decyl-9[8]-xanthogenate; and

a modulator of cellular glutathione effective to decrease cellular glutathione levels.

50. (New) The composition of claim 49, wherein the modulator of cellular glutathione is selected from the group consisting of ethacrynic acid, L-buthionine-S,R-sulfoximine, diethylmaleate, 2-cyclohexene-1-one, and 1-chloro-2,4-dinitrobenzene.

51. (New) The composition of claim 49, wherein the modulator of cellular glutathione is ethacrynic acid.

52. (New) The composition of claim 49, further comprising dimethylethanolamine.

53. (New) The composition of claim 49, further comprising a metal cation selected from the group consisting of Zn^{++} and Cu^{++}.

54. (New) The composition of claim 53, wherein the metal cation is Zn^{++}.

55. (New) The composition of claim 49, wherein the modulator of cellular glutathione is ethacrynic acid, and wherein the composition further comprises dimethylethanolamine and Zn^{++}.

REMARKS

The above listed claim amendments along with the following remarks are fully responsive to the Office Action set forth above. By this Amendment, claims 1-4 and 10 are amended, claims 5, 9, and 11-30 are cancelled, and new claims 31-55 are added. After entry of this Amendment, claims 1-4, 6-8, 10, and 31-55 are pending. No new matter is added by the amendments or the new claims.

The Applicant hereby affirms the election of Group I, claims 1-10 and 26-30. Claims 11-25 of Group II were withdrawn from consideration by the Examiner, and are now cancelled.

The specification is amended at page 1 to contain a reference to a previously filed U.S. provisional application, the benefit of which is claimed by the present application under 35 U.S.C. § 119(e). The present application does not claim priority to any application under 35 U.S.C. § 120. The amendment to the specification is sufficient to overcome the Examiner's objection to the priority claim and the Examiner's objection to the Applicant's declaration.

The specification is amended for the sake of clarity at page 3 and page 11 to properly reflect conventional notation for the generic structure of the dithiocarbonyl compounds useful in the present invention. The generic structure includes both a carbon-sulfur double bond and a carbon-sulfur single bond: $(R_1)(R_2)Z-C(S)-S-Y$. The clarification is also reflected in claim 2 as presently amended.

The specification is also amended at page 15 to insert the proper generic structure for suitable dimers of dithiocarbamate monomers: $(R_1)_m(R_2)Z-C(S)-S-S-C(S)-Z(R_1)_m(R_2)$. The generic structure properly represents Disulfuram (CAS 97-77-8), a dimer included in the composition of Example 5, for instance.

The specification is amended at various points on pages 25-40 to correct numbering for several of the Examples.

No new matter is introduced by the amendments to the specification.

Support for new claim 31, and the claims that depend therefrom, may be found in the specification at page 17 lines 5-8 and 12-15, and in at least Examples 5, 6, 7, 8, 10, 17, and 18.

Support for new claim 39, and the claims that depend therefrom, may be found in the specification at page 17, lines 16-19, and in at least Examples 5, 6, 9, 12, and 13.

Support for new claim 46, and the claims that depend therefrom, may be found in the specification in at least Examples 5 and 6.

Support for new claim 49, and the claims that depend therefrom, may be found in the specification in at least Examples 6, 7, 8, and 14, and in the claims as originally filed.

Claim Rejections – 35 U.S.C. § 112

The Examiner has rejected claims 1-9 and 26-30 as not enabled by the specification. Claims 5, 9, and 26-30 are now cancelled.

Claim 1 presently recites a composition comprising a dithiocarbamate compound, a metal cation selected from the group consisting of Zn^{++} and Cu^{++}, a modulator of cellular glutathione effective to decrease cellular glutathione, and dimethylethanolamine.

Claim 1 is amended to recite that the claimed composition includes a dithiocarbamate compound. The term "dithiocarbamate" as used by the Applicant in the claims is intended to include both dithiocarbamate monomers and dimers of dithiocarbamate monomers, such as Disulfuram. The Examiner stated at page 7 of the Office action that the specification is enabling for compositions including dithiocarbamate compounds.

Claim 1 is also amended to recite that the metal cation is selected from the group consisting of Zn^{++} and Cu^{++}. Claim 1 is further amended to recite that the composition includes dimethylethanolamine.

Claim 1 is amended to recite that the modulator of cellular glutathione is effective to decrease cellular glutathione levels. Support for this amendment may be found in the specification at page 15, line 26 bridging to page 16, line 7. Several compounds that are effective to decrease cellular glutathione, including ethacrynic acid, L-buthionine-S,R-sulfoximine, diethylmaleate, 2-cyclohexene-1-one, and 1-chloro-2,4-dinitrobenzene, are disclosed in the specification. Others are known in the art. It is submitted by the Applicant

that the present invention as recited in claim 1 is not limited to any one of the listed chemicals, but encompasses compositions that include chemicals which act as modulators of cellular glutathione and are effective to decrease cellular glutathione levels, in combination with the other recited chemotherapeutic agents. The identification of modulators of cellular glutathione effective to decrease cellular glutathione levels is within the skill of the ordinary artisan.

It is respectfully submitted that claim 1 as presently amended is properly enabled by the specification. 35 U.S.C. § 112, first paragraph, requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In Re Fisher*, 427 F.2d 833 (CCPA 1970). The enablement requirement is satisfied when the specification teaches those in the art to make and use the invention without undue experimentation. *In re Vaeck*, 20 USPQ.2d 1438 (CAFC 1991).

It is submitted by the Applicant that a person of ordinary skill in the art would be able to practice the invention as claimed in claim 1, without undue experimentation. A person would readily be able to practice numerous embodiments of the invention as claimed in claim 1, by performing in a straightforward fashion the routine experiments described in the specification at page 23, line 11 to page 24, line 25. Withdrawal of the rejection is requested.

In view of the amendments to claim 1, claim 2 is accordingly amended to recite a generic formula for only dithiocarbamate compounds. Furthermore, claim 3 is amended to remove the recitation of tricyclo-[5.2.1.$O^{2,6}$]-decyl-9[8]-xanthogenate (commonly known as D609), which is not a dithiocarbamate compound. Accordingly, claims 49-55, which are directed to compositions comprising to tricyclo-[5.2.1.$O^{2,6}$]-decyl-9[8]-xanthogenate in combination with other chemotherapeutic agents, have been added.

Claim Rejections – 35 U.S.C. § 103

The Examiner rejected claim 28 as unpatentable over Lacreta, *et al.* in view of Crescenti. Claim 28 is cancelled. Withdrawal of the rejection is requested.

Conclusion

All pending claims are now in condition for allowance. A notice to that effect is respectfully requested.

Respectfully Submitted,

ZOLTAN KISS

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Dated: July 20, 2003

M2:20552658.01

Serial No.: 09/864,685

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	ZOLTAN KISS	**Examiner:**	Frederick Krass
Serial No.:	09/864,685	Group Art Unit:	1614
Filed:	May 24, 2001		
For:	METHODS AND COMPOSITIONS FOR THE TREATMENT OF HUMAN AND ANIMAL CANCERS	Docket No.	54938-236531

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I CERTIFY THAT, ON OCTOBER 22, 2003, THIS PAPER IS BEING TRANSMITTED VIA FACSIMILE TO 703.872.9307, MAIL STOP AFTER FINAL, COMMISSIONER FOR PATENTS, P. O. BOX 1450, ALEXANDRIA, VA 22313-1450.

Karen Hull
Karen Hull

AMENDMENT

This Amendment is responsive to the outstanding final Office Action mailed October 7, 2003. This Amendment places the application in condition for allowance, or in better position for appeal, and entry of this Amendment and reconsideration of the application is requested.

The Applicant wishes to remind the Examiner that a Petition to Make Special has been granted for the present application. Prompt attention to this application is respectfully requested and appreciated.

No fee is included with this paper. In the event that a fee is required for entry of this paper, the Commissioner is authorized to charge our Deposit Account 06-0029 and is requested to notify us of the same.

This Amendment includes:

1) Amendments to the Claims (pp. 2-6)

2) Remarks and Conclusion (pp. 7-8)

AMENDMENTS TO THE CLAIMS

1. (Currently amended) A composition capable of inducing apoptosis or necrosis in cancer cells, comprising:

a dithiocarbamate compound;

a metal cation selected from the group consisting of Zn^{++} and Cu^{++};

a modulator of cellular glutathione effective to decrease cellular glutathione levels, wherein the modulator of cellular glutathione is selected from the group consisting of ethacrynic acid, L-buthionine-S,R-sulfoximine, diethylmaleate, 2-cyclohexene-1-one, and 1-chloro-2,4-dinitrobenzene; and

dimethylethanolamine.

2. (Currently amended) The composition of claim 1, wherein the dithiocarbamate compound has the formula:

$(R_1)(R_2)N-C(=S)-S-Y$,

wherein R_1 and R_2 may be independently selected from the group consisting of hydrogen, C1-C24 straight, branched, or cyclic alkyl, alkenyl, aryl, acyl, alkaryl, aralkyl, and alkoxy groups, optionally substituted with ester, ether, halogen, sulfate, hydroxy, or phosphate groups, and wherein R_1 and R_2 may be optionally connected via a bridge comprising $-(CH_2)_n-$, wherein n is 3-8, and wherein said bridge may be optionally substituted independently on any of the carbon atoms with C1-C10 straight, branched, or cyclic alkyl, aryl, ~~aryalkyl~~ aralkyl, or alkaryl groups, each of said groups optionally substituted with hydroxy, halo, phosphate, sulfate, or sulfonate groups; and

wherein Y is chosen from the group consisting of hydrogen, a pharmaceutically acceptable cation, a physiologically cleavable leaving group, a targeting moiety, and a chemotherapeutic drug.

3. (Previously presented) The composition of claim 1, wherein the dithiocarbamate compound is selected from the group consisting of: diethyldithiocarbamate; tetraethylthiuram disulfide; and pyrrolidinedithiocarbamate.

4. (Currently amended) The composition of claim 1, wherein the dithiocarbamate compound is pyrrolidinedithiocarbamate.

5. (Cancelled)

6. (Currently amended) The composition of claim 1, wherein the metal cation is ~~Zn^{2+}~~ Zn^{++}.

7. (Cancelled)

8. (Original) The composition of claim 1, wherein the modulator of cellular glutathione is ethacrynic acid.

9. (Cancelled)

10. (Currently amended) The composition of claim 1, wherein the dithiocarbamate compound is pyrrolidinedithiocarbamate in a concentration range of about 5-200 μM, wherein the metal cation is ~~Zn^{2+}~~ Zn^{++} in a concentration range of about 20-500 μM, wherein the modulator of cellular glutathione is ethacrynic acid in a concentration range of about 10-300 μM, and wherein dimethylethanolamine is in a concentration range of about 3-40 mM.

11. – 30. (Cancelled)

31. (Currently amended) A composition capable of inducing apoptosis or necrosis in cancer cells, comprising:

a biologically effective amount of a dithiocarbamate compound; and

a biologically effective amount of a modulator of cellular glutathione effective to decrease cellular glutathione levels, wherein the modulator of cellular glutathione is selected from the group consisting of ethacrynic acid, L-buthionine-S,R-sulfoximine, diethylmaleate, 2-cyclohexene-1-one, and 1-chloro-2,4-dinitrobenzene.

32. (Previously presented) The composition of claim 31, wherein the dithiocarbamate compound is pyrrolidinedithiocarbamate.

33. (Cancelled)

34. (Previously presented) The composition of claim 31, wherein the modulator of cellular glutathione is ethacrynic acid.

35. (Previously presented) The composition of claim 31, wherein the dithiocarbamate compound is pyrrolidinedithiocarbamate, and the modulator of cellular glutathione is ethacrynic acid.

36. (Previously presented) The composition of claim 35, comprising about 10 to about 50 μM pyrrolidinedithiocarbamate, and about 10 to about 50 μM ethacrynic acid.

37. (Previously presented) The composition of claim 35, comprising about 20 μM pyrrolidinedithiocarbamate, and about 10 μM ethacrynic acid.

38. (Previously presented) The composition of claim 31, further comprising a biologically effective amount of dimethylethanolamine.

39. (Currently amended) A composition capable of inducing apoptosis or necrosis in cancer cells, comprising:

a biologically effective amount of a dithiocarbamate compound;

a biologically effective amount of a modulator of cellular glutathione effective to decrease cellular glutathione levels, wherein the modulator of cellular glutathione is selected from the group consisting of ethacrynic acid, L-buthionine-S,R-sulfoximine, diethylmaleate, 2-cyclohexene-1-one, and 1-chloro-2,4-dinitrobenzene; and

a biologically effective amount of a metal cation selected from the group consisting of Zn^{++} and Cu^{++}.

40. (Previously presented) The composition of claim 39, wherein the dithiocarbamate compound is pyrrolidinedithiocarbamate.

41. (Cancelled)

42. (Previously presented) The composition of claim 39, wherein the modulator of cellular glutathione is ethacrynic acid.

43. (Previously presented) The composition of claim 39, wherein the metal cation is Zn^{++}.

44. (Previously presented) The composition of claim 39, comprising about 5 to about 50 μM pyrrolidinedithiocarbamate, about 50 to about 200 μM Zn^{++}, and about 10 to about 100 μM ethacrynic acid.

45. (Previously presented) The composition of claim 39, comprising about 10 to about 50 μM pyrrolidinedithiocarbamate, about 30 to about 80 μM Zn^{++}, and about 30 to about 80 μM ethacrynic acid.

46. (Previously presented) A composition capable of inducing apoptosis or necrosis in cancer cells, comprising:

a biologically effective amount of a dithiocarbamate compound;

a biologically effective amount of a metal cation selected from the group consisting of Zn^{++} and Cu^{++}; and

a biologically effective amount of dimethyethanolamine.

47. (Previously presented) The composition of claim 46, wherein the dithiocarbamate compound is pyrrolidinedithiocarbamate.

48. (Previously presented) The composition of claim 46, wherein the metal cation is Zn^{++}.

49. (Currently amended) A composition capable of inducing apoptosis or necrosis in cancer cells, comprising:

tricyclo-[5.2.1.$O^{2,6}$]-decyl-9[8]-xanthogenate; and

a modulator of cellular glutathione effective to decrease cellular glutathione levels, wherein the modulator of cellular glutathione is selected from the group consisting of ethacrynic acid, L-buthionine-S,R-sulfoximine, diethylmaleate, 2-cyclohexene-1-one, and 1-chloro-2,4-dinitrobenzene.

50. (Cancelled)

51. (Previously presented) The composition of claim 49, wherein the modulator of cellular glutathione is ethacrynic acid.

52. (Previously presented) The composition of claim 49, further comprising dimethylethanolamine.

53. (Previously presented) The composition of claim 49, further comprising a metal cation selected from the group consisting of Zn^{++} and Cu^{++}.

54. (Previously presented) The composition of claim 53, wherein the metal cation is Zn^{++}.

55. (Previously presented) The composition of claim 49, wherein the modulator of cellular glutathione is ethacrynic acid, and wherein the composition further comprises dimethylethanolamine and Zn^{++}.

REMARKS

The above-listed claim amendments along with the following remarks are fully responsive to the final Office Action set forth above. This Amendment places the application in condition for allowance, or in better position for appeal, and entry of this Amendment and reconsideration of the application is requested.

By this Amendment, claims 1, 2, 4, 6, 10, 31, 39, and 49 are amended. Claims 2, 4, 6, and 10 are amended only to correct typographical errors. No new matter is introduced into the application by the claim amendments. Claims 7, 33, 41, and 50 are cancelled. After entry of this Amendment, claims 1-4, 6, 8, 10, 31, 32, 34-40, 42-49, and 51-55 are pending. The Examiner indicated that claims 46-48 are allowable, and that claims 7, 8, 10, 33-37, 41-45, 50, 51, and 55 would be allowable if rewritten in independent form.

Claim Rejections – 35 U.S.C. § 112

The Examiner rejected claims 1-4, 6, 31, 32, 38-40, 49 and 52-54 under 35 U.S.C. § 112, as being broader than the scope of enablement provided by the disclosure. The Examiner states that the claims are not adequately enabled for the term "modulator of cellular glutathione effective to decrease cellular glutathione levels."

The Examiner did not reject any claims in which a specific chemical entity was named as the modulator of cellular glutathione levels. Rather, the Examiner objected to such claims, and indicated that those claims would be allowable if written in independent form.

The Applicant respectfully differs with the Examiner regarding the scope of enablement provided by the disclosure. However, in the interests of expediting prosecution, independent claims 1, 31, 39, and 49 are amended to recite that the modulator of cellular glutathione is selected from the group consisting of ethacrynic acid, L-buthionine-S,R-sulfoximine, diethylmaleate, 2-cyclohexene-1-one, and 1-chloro-2,4-dinitrobenzene. Claims 7, 33, 41, and 50 are accordingly cancelled.

The present claim amendments are not a disclaimer of scope of the claimed invention. The Applicant reserves the right to pursue, by way of a continuation application, claims that are not limited to the recited modulators of cellular glutathione levels.

Withdrawal of all rejections is requested.

Conclusion

This Amendment places the application in condition for allowance, or in better position for appeal, and entry of this Amendment and reconsideration of the application is requested. After entry of this Amendment, all claims are in condition for allowance and a notice to that effect is respectfully requested.

Respectfully Submitted,

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Dated: October 22, 2003

M2:20578452.01